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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/767,370	01/23/2001	Jeffrey Browning	A054 US	2716

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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/767,370	BROWNING ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *25 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *1-7,12-15,20-25 and 30-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11,16-19 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II, claims 8-11, 16-19,and 26-29 in Paper No. 13 is acknowledged. Claims 1-36 are pending, claims 1-7, 12-15, 20-25, and 30-36 are withdrawn from consideration as being drawn o a non-elected invention. Therefore claims 8-11, 16-19, and 26-29 are examined on the merits.

Information Disclosure Statement

2. The Information Disclosure Statement filed 1/09/02 (paper no. 10) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Specification

3. The disclosure is objected to because of the following informalities: The numbering of each of the figure legends in the Brief Description of Drawings section must match each of the labeled figures. For example, Figure 5 should be amended to Figure 5A-5C.

Appropriate correction is required.

Drawings

4. The Figure legend and drawings are objected to because the figure legend recites a figure 11a, however, there is no figure present in the instant application. Correction is required.

Claim Rejections - 35 USC § 112

5. Claims 8-11, 16-19, and 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Regarding claims 8,16, 26, and dependent claims thereof, in the recitation of the phrase, *"active protein"*, it is unclear whether this is meant to distinguish a type and/or frequency of protein, the expression level, or the state of the protein's functionality. Absent disclosure of the particular activities by which active proteins are to be measured, the metes and bounds of the claimed invention cannot be determined. Correction and clarification is required.

7. Regarding claim 16 in the recitation of *"the protein-Ig fusion"*, it is unclear as to which protein fusion is being referred.

8. Regarding claims 8-11, 16-19, and 26-29 in the recitation of the term *"fusion"*, it is unclear as to the metes and bounds of the term, because it is unclear as to what kind of fusion is being refered (i.e. is it a fusion protein?).

9. Regarding claims 8,16,26, and dependent claims thereof the phrase "about" renders the claim indefinite because the metes and bounds of the claimed range cannot be determined.

10. Regarding claims 10-11, 18-19, and 28-29 in the recitation of the term *"fragment"*, it is unclear as to the exact meaning of this term because the metes and bounds of the claimed invention cannot be determined due to a lack of an adequate definition in the specification.

11. Regarding claims 11, 19, and 29 in the recitation of the term/abbreviation *"HVEM"*, it is unclear as to the meaning of this term/abbreviation. This rejection can be overcome by including at the first recitation of the term/abbreviation in the claims, the full name of the abbreviation.

Claims 10, 11, 18, 19, 28, and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth LT-β receptor and therefore the written description is not commensurate in scope with the claims which read on fragments of LT- β receptor.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of LT- β receptor the skilled artisan cannot envision the detailed structure of the encompassed fragments. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc.*

V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn specifically drawn to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". The present claims are drawn to a genus comprising fusion proteins incorporating an LT- β receptor of HVEM and fragments of LT- β receptors or HVEM.

The specification discloses fusion proteins comprising LT-β receptor and any portion of an immunoglobulin protein. No disclosure, beyond the mere mention of fragments is made in the specification for any of the other species of the claimed genus. There is no disclosure of any common structural features for the encompassed fragments. Therefore, there is substantial variability among the species. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only a fusion of LT-β receptor and Ig proteins/molecules meet the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 101

12. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claims 11, 19, and 29 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The disclosed utilities for the HVEM protein include the treatment of immunological disease, including in vitro immune function. However, neither the specification nor any art of record teaches what the HVEM is, how it functions, or a specific and well-established utility claimed. Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement in the etiology of any specific disease. The asserted utility of the HVEM protein is based on the assertion that HVEM belongs to the TNF family (page 3, line 28-31, page 4, lines 1-2).

The specification further proposes, that HVEM protein will have similar biological effects and activities to other TNF family members (page 3, line 28-31). However, evidence based on protein sequence homology does not alone permit extrapolation to an isolated amino acid's biological function or use thereof. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry

out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride

and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Thus, even though the HVEM protein may belong to the TNF family of proteins, there may still be a difference in functionality, and it cannot be predicted, based on the information in the specification, what affect this difference has on the function of the protein. Further even if HVEM belongs to the TNF family, neither the specification nor any art of record teaches what the protein is, what it does, nor teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active as claimed in a pharmaceutical composition.

In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard

to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Scott et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, any dissimilarity, to the TNF family, the function of the HVEM protein could not be predicted, based on sequence similarity with TNF family.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide and fragments thereof. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claims 11, 19, and 29 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Crowe *et al* (Science 1994 Apr 29;264(5159):707-710) in light of Crowe *et al* (J. Immunol Methods 1994 Jan 12;168(1):79-89). Claims 8-10 are drawn to an active protein-Ig fusion protein, wherein the fusion comprises a member of the TNF family, and wherein the TNF family member if LT- β receptor. Claims 8-10 are further drawn to an active protein-Ig fusion that is cultured in a host transformed with DNA encoding the fusion in a culture system having a temperature range from 27°C to 35°C. Crowe *et al* (Science) disclose a fusion protein comprising a TNF family member, namely LT- β, and a portion of an immunoglobulin. However, Crowe *et al* (Science) do not specifically disclose of temperature ranges but makes reference to an earlier article Crowe *et al* (J. Immunol Methods) which does specifically disclose culturing a host cell transformed with a DNA encoding the fusion at a temperature range of 27°C.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
August 7, 2002

Brenda Brumback
BRENDA BRUMBACK
Primary PATENT EXAMINER